Eur J Vasc Endovasc Surg **26**, 1–16 (2003)
doi:10.1053/ejvs.2002.1927, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

REVIEW

Antiplatelet Therapy in Peripheral Arterial Disease. Consensus Statement

Peripheral Arterial Diseases Antiplatelet Consensus Group

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Objectives: *Antiplatelet agents are commonly prescribed to reduce the risk of myocardial infarction, stroke and graft occlusion in patients with peripheral arterial disease (PAD). The objective was to summarise current evidence and provide recommendations on the use of antiplatelet agents in PAD.*
Methods: *A consensus group was assembled including 20 specialists from a variety of fields involved in the management of patients with PAD. Data was circulated in a systematic manner prior to a main consensus meeting held in November 2001. The document subsequently produced was circulated within the group to ensure agreement in the interpretation and presentation of its findings.*
Results: *Consensus recommendations are provided in 7 common or contentious scenarios in PAD. The recommendations are graded to reflect the evidence available and interpretations of the group. Although the document provides recommendations, it is stressed that they must be interpreted in the light of individual patient circumstances.*
Conclusion: *Antiplatelet agents have an important role in the management of patient with PAD. Although this document provides consensus recommendations, the optimum treatment in many scenarios remains unclear due to a lack of focussed clinical trials in PAD.*

Key Words: Antiplatelet therapy; Peripheral arterial disease; Vascular surgery; Angioplasty; Consensus.

Introduction

Peripheral arterial disease (PAD) is a major healthcare problem and is associated with a significant increase in the risk of myocardial infarction (MI) and stroke.[1] Intermittent Claudication (IC) is the commonest manifestation of PAD and is present in approximately 4% of those over 50 years.[2,3] In itself IC is a relatively benign condition with less than 5% of patients per 5 years deteriorating and requiring peripheral arterial intervention.[4,5] In the Systolic Hypertension in the Elderly Program, the age adjusted relative risk of death with an ankle brachial pressure index (ABPI) <0.9 was 3.0 in men and 2.67 in women.[6] The results were similar for cardiovascular mortality and persisted even after adjustment for other cardiovascular risk factors and are similar to findings in other studies.[7,8]

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Evidence from meta-analyses confirms that the long-term use of antiplatelet agents reduces the rate of MI and ischaemic stroke in patients with symptomatic PAD;[9–11] however, there are many "scenarios" in vascular surgery where this evidence is less strong and with the emergence of newer agents, additional questions arise relating to efficacy and cost. In addition, strong evidence is not available on the effectiveness of antiplatelet drugs in the perioperative period, raising concerns as to whether the risk of bleeding outweighs the benefits produced by inhibition of thrombosis.

With the development of newer antiplatelet agents and the constant generation of new evidence concerning antiplatelet therapy, clinical decision-making can be difficult. In order to summarise current data, and consider contentious issues of management, a consensus group was organised. The group aimed to summarise current evidence concerning antiplatelet agents in patients with PAD, and generate guidelines for use in hospital and the community (Fig. 1). Specific attention was given to providing clarity in contentious

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- To provide medical practitioners from all fields with evidence based recommendations on the use of antiplatelet therapy in peripheral arterial disease patients.
- Where strong evidence does not exist or is awaited, to provide guidelines that are sensible, safe and effective.
- To identify areas where evidence is deficient and further research is required.

Fig. 1. Aims of the consensus meeting.

1. Intermittent claudication (IC)
2. Critical limb ischaemia (CLI)
3. Angioplasty / stenting in peripheral arteries
4. Peripheral bypass grafting
5. Abdominal aortic aneurysm
6. Recurrent vascular events
7. Patients taking non-aspirin NSAIDs

Fig. 2. Clinical scenarios considered.

areas (Fig. 2). The document can also be used as a reference for other health professionals managing patients with PAD. In addition, controversy exists over the management of patients with recurrent vascular events and those intolerant of aspirin. The consensus group was organised to address some of these issues.

Methods

Organisation of the conference

The organisers of the conference used their experience of previous similar conferences and also sought guidance from the "Heath Technology Assessment" review of "Consensus development methods, and their use in clinical guideline development".[12] The main consensus meeting was held on the 2nd and 3rd of November 2001.

Participants were selected from defined specialist categories involved in the management of patients with PAD and its associated disorders, including specialists in trial design and epidemiology. The key consensus questions were judged to be representative of common clinical scenarios in PAD and identified at an early stage in the process (Fig. 2). Review-based evidence was provided prior to the consensus meeting and participants were encouraged to bring further data identified outside the review. During the meeting information was presented in an open manner followed by a structured assimilation of the findings, giving all participants a chance to voice their opinion. For each meeting session two facilitators from differing specialities were selected. The meeting timetable provided scope to discuss matters arising, thus avoiding the pressure to make decisions without carefully considering the evidence.

Evidence considered

The literature considered for this document was identified from electronic databases and from references cited in important publications. Data deemed suitable to consider for the consensus process came from meta-analyses, systematic reviews, randomised controlled trials, and cohort and cross-sectional studies. When appraising the evidence well conducted randomised controlled trials and meta-analyses were most highly ranked. Key references were available for consultation during the meeting. In areas where there was insufficient data to produce evidence based recommendations, conclusions were drawn using the limited scientific data that is available and the personal expertise and experience of the participants. Evidence was graded to reflect these deficiencies so as not to mislead the reader. From the outset it was clear that identifying areas where evidence is deficient and suggesting where further research is required was an important role of the meeting.

Grading of evidence and strength of recommendations

We elected to appraise evidence and grade strength of recommendations using systems advocated by Michaels *et al*.[13] We would like to emphasise that the letters and numbering used in these systems may not directly relate to other evaluation systems in operation. (Fig. 3).

Scenario 1

Antiplatelet agents in patients with intermittent claudication (Fig. 4)

Evidence

There is considerable evidence that PAD is a marker of coronary and cerebrovascular disorders, and that patients with PAD should be considered as a "high risk group" for stroke and MI.[2,14,15] Studies have demonstrated that approximately half the patients

Grading of Evidence

Grade I. **"Beyond reasonable doubt"**
Evidence from high quality randomized controlled trials, systematic reviews, or large observational data-sets which is directly applicable to the specific population of concern and has clear results.

Grade II. **"On the balance of probabilities"**
Evidence of 'best practice' from a high quality review of the literature, which fails to reach the highest standard of proof due to heterogeneity, questionable trial methodology or lack of evidence in the population to which the guidelines apply.

Grade III. **"Unproven"**
Contradictory evidence or insufficient evidence upon which to base a decision.

Strength of recommendations

A. A strong recommendation, which should be followed unless there are compelling reasons not to do so.

B. Recommendation based on evidence of effectiveness that may need interpretation in the light of other factors (e.g. patient preferences, local facilities, local audit results or available resources)

C. Recommendations where there is inadequate evidence on effectiveness but pragmatic or financial reasons to institute an agreed policy.

Fig. 3. Grading of evidence and strength of recommendations.

Summary of evidence:

- Peripheral arterial disease is a marker of generalised cardiovascular risk. (I)
- Antiplatelet agents reduce cardiovascular events and death in patients with intermittent claudication. (I)
- Clopidogrel is more effective than aspirin in preventing vascular events (overall 8.7% proportional reduction in risk). (I)
- Aspirin 75-325 mg daily seems effective (I), and has lower side effects than an aspirin dose >325 mg. (II)

Recommendations:

- All patients with intermittent claudication or who have had previous vascular intervention should be considered for long-term anti-platelet therapy. (A)
- The agents used should be either Aspirin 75-325 mg daily (A) or Clopidogrel 75 mg per day. (A)

Fig. 4. Scenario 1: Antiplatelet agents in patients with intermittent claudication.

with symptomatic PAD also have evidence of IHD,[16] and have almost a twofold increase in mortality, predominantly from ischaemic heart disease and stroke.[3,17,18] When examining the supportive evidence for the use of antiplatelet drugs in patients with PAD we have three main sources of evidence to consider; firstly studies comparing agents to placebo, secondly studies comparing one agent against another, and

Table 1. Placebo controlled studies in stable claudicants assessing vascular events.[9]

Antiplatelet Drug	Numbers of patients
Aspirin[19]	258
Aspirin plus Dipyriamole[20–23]	471
Ticlopidine[24–26,28–30]	1990
Picotamide[31]	2304

Studies with vascular events as part of the primary endpoints.

Table 2. Studies comparing different antiplatelet regimes in PAD.

Study	Antiplatelet agents compared	Numbers of patients
CAPRIE* 1996[36]	Clopidogrel vs Aspirin	6452 (with IC)
Hess 1985[23]	Aspirin vs Aspirin plus Dipyridamole	240
Libretti 1986[37]	Aspirin vs Aspirin plus Dipyridamole	54
Schoop 1983[38,39]	Aspirin vs Aspirin plus Dipyridamole	300
Schoop 1983[40]	Aspirin vs Ticlopidine	62

*CAPRIE was the only PAD study to assess vascular events in its outcome measures.

thirdly extrapolation of data from trials in IHD and CVD. Over the last 10 years it has become accepted that antiplatelet drugs are effective in reducing cardiovascular mortality and morbidity in patients with vascular disease, and consequently placebo controlled studies have become effectively unethical. Current studies now focus on comparing new agents against existing treatment, such as aspirin.

Antiplatelet vs placebo studies in PAD (Table 1[9,19–31])

In IHD and CVD there is now little disagreement that patients benefit from antiplatelet therapy, with aspirin being first choice for general prophylaxis.[32,33] Considering all antiplatelet drugs together there is now strong evidence confirming the benefits of antiplatelet agents in reducing MI, stroke and vascular death in patients with symptomatic PAD, as confirmed by the ATTC[34] and the systematic review by Robless *et al*.[9] Both studies demonstrated an approximate 25% reduction in all vascular events. Although in antiplatelet studies of patients with IHD and CVD a large proportion of data for meta-analyses comes from trials of aspirin, in PAD the actual number of suitable trials of aspirin versus placebo is small. Therefore, the results of meta-analyses of antiplatelet agents in PAD are much more dependent on drug trials involving picotamide and the thienopyridines. There have been no randomised, blinded, placebo controlled trials of dipyridamole alone in the prevention of vascular events. Picotamide has been demonstrated to be an effective antiplatelet agent compared with placebo, but no clinical trials have shown it to be more effective than current antiplatelet agents. Despite increasing walking distance, Cilostazol has not been demonstrated to be more effective than placebo in reducing MI in claudicants.[35]

Comparison of one antiplatelet against another in PAD

In the five trials of one antiplatelet regime against aspirin there appeared to be a benefit for the second agents with the biggest effect shown in the CAPRIE study. Overall in CAPRIE there was a relative risk reduction in outcome events of 8.7% (CI 0.3–16.5; $p = 0.043$) in favour of clopidogrel over aspirin. In the PAD subgroup the relative risk reduction was greater at 23.8% (CI 8.9–36.2; $p = 0.0028$)[36] (Table 2[23,36–40]).

Risk of bleeding complications with long term use of antiplatelet agents

Aspirin is the most widely used antiplatelet agent and data from the ATTC suggests that doses less than 325 mg are equally as effective as higher doses.[34] It has been established that there is a small but significant increase in bleeding complications with long-term aspirin use, and the trend has been towards prescribing lower doses of aspirin. Despite this tendency, and the conflicting results of individual trials comparing aspirin doses, a large meta-analysis was unable to demonstrate a significant reduction in bleeding complications with these lower doses of aspirin.[41–43] The study also concluded that aspirin therapy should only be instituted if the risk of vascular events $>1.5\%$ per year for benefit to outweigh risk.[43]

Most of the data on the relative safety of clopidogrel comes from the "Clopidogrel vs Aspirin in Patients at risk of Recurrent Ischaemic Events study" (CAPRIE), comparing aspirin 325 mg OD with clopidogrel 75 mg OD.[36] In this study the frequency of GI haemorrhage and upper GI symptoms were significantly lower in patients on clopidogrel than those on aspirin. A study in cardiac disease has shown that when aspirin is combined with clopidogrel the relative risk of major bleeding was increased 1.38 (CI 1.13–1.67); however there was no statistically significant excess in fatal bleeding or bleeding requiring surgical intervention.[44]

There is no clear evidence that dipyridamole alone increases bleeding, although headache, its commonest side effect may require drug withdrawal. In the European Stroke Prevention Study 2 (ESPS-2), dipyridamole alone showed no increase in rates of adverse bleeding when compared with placebo; however, patients treated with aspirin alone or aspirin plus dipyridamole had higher rates of adverse bleeding than the placebo treated group.[45]

Recommendations

Patients with a diagnosis of symptomatic PAD, preferably confirmed by an ABPI <0.90, should receive antiplatelet therapy. This includes asymptomatic patients who have previously undergone intervention for symptomatic disease. The 2002 ATTC demonstrated that aspirin at doses of 75–150 mg appears to be at least as effective as aspirin at higher doses in high-risk patients.[34] There is little information on the value of antiplatelet agents in those patients with an ABPI <0.9 who are asymptomatic; however, they are at high risk of vascular events. When dipyridamole is prescribed, it is recommended that it is given in combination with aspirin.

There is evidence that the thienopyridines (clopidogrel and ticlopidine) are more effective than aspirin alone. In direct comparisons with aspirin, there was an odds reduction in vascular events of 10% favouring clopidogrel, and 12% favouring ticlopidine. Furthermore, if one combines the indirect comparisons using 43 trials of ticlopidine against control (32% odds reduction) and the 65 trials of aspirin against control (23% odds reduction), the derived odds reduction for ticlopidine versus aspirin is 10.5%. This is entirely consistent with the estimate from direct comparisons and strengthens the evidence of superiority of the thienopyridines over aspirin. While clopidogrel and ticlopidine appear equally efficacious, the safety profile of clopidogrel is markedly better and one can no longer justify the use of ticlopidine. However, aspirin is the agreed first line treatment for secondary prevention in IHD in the U.K. as it is both effective and cheap.[32,33] With these cost-benefit issues the choice between aspirin and clopidogrel is likely to remain contentious until further data emerges.

Scenario 2

Antiplatelet agents in patients with critical limb ischaemia (CLI) (Fig. 5)

Evidence

There are no published trials showing that oral antiplatelet drugs improve limb salvage in patients with CLI. Patients with CLI are at high risk of MI and stroke, therefore providing a justification for antiplatelet prophylaxis. Whenever possible CLI should be managed with surgical or endovascular intervention and these scenarios are covered in the appropriate sections of this document, as are the risks of bleeding associated with the use of antiplatelet agents.

Recommendation

As with patients with IC, those with CLI should be treated with antiplatelet therapy for reduction of cardiovascular risk, with the choice being between aspirin and clopidogrel.

Scenario 3

Antiplatelet therapy in angioplasty and stenting in peripheral arteries (Fig. 6)

Evidence

In patients undergoing peripheral arterial angioplasty and stenting, issues arise regarding the risk and benefit of antiplatelet therapy. Antiplatelet therapy can reduce arterial thrombosis in the target vessel, coronary and cerebrovascular circulation, but carries the risk of increasing bleeding complications.

Summary of evidence:

- Patients with critical limb ischaemia are at high risk of subsequent cardiovascular events especially MI and stroke. (II)
- There is no compelling published data that antiplatelet agents alter the outcome for the limb in patients with critical limb ischaemia. (II)

Recommendations:

- All patients with critical limb ischaemia, or who have had previous vascular intervention should be considered for long-term anti-platelet therapy (A)
- The agents used should be either Aspirin 75-325 mg daily (A) or Clopidogrel 75 mg per day (A)

Fig. 5. Scenario 2: Antiplatelet agents in patients with critical limb ischaemia.

Summary of evidence:

- Patients undergoing vascular radiological intervention are at high risk of subsequent MI and stroke. (I)
- Continuing antiplatelet agents around the time of vascular intervention may reduce the risk of periprocedure MI. (III)
- There is limited evidence, extrapolated from cardiac angioplasty and stenting that antiplatelet agents increase bleeding complications from percutaneous arterial puncture sites. (III)
- There is limited evidence that antiplatelet agents reduce restenosis. (III)

Recommendations:

- All patients with symptomatic peripheral arterial disease or who have had previous vascular intervention should be considered for long-term anti-platelet therapy, unless contraindicated (A)
- Aspirin should be continued peri-procedure unless a particular concern over increased bleeding exists. (B)
- Consideration should be made to stopping clopidogrel 5 days prior to elective surgery. (C)

Fig. 6. Scenario 3: Antiplatelet therapy in angioplasty and stenting in peripheral arteries.

Reduction in cardiovascular events. In comparison with operative surgery the cardiovascular mortality is lower in patients undergoing peripheral angioplasty.[46,47] There is no good data demonstrating that antiplatelet drugs reduce periprocedure cardiovascular events.

Target vessel occlusion. A systematic review by Watson *et al*.[48] of antiplatelet agents in peripheral angioplasty and stenting was unable to demonstrate that antiplatelet drugs reduce the rate of target vessel re-occlusion. The review was limited by the scarcity of good quality trials of antiplatelet drugs in patients undergoing peripheral angioplasty. In coronary angioplasty and stenting large trials have demonstrated the benefits of antiplatelet agents, and also that different agents can act synergistically.[44,49,50] For patients not on an antiplatelet treatment it is suggested that a 300 mg dose of aspirin should be given at least 2 h prior to the procedure. If lower doses are used potential delays in bio-availability may occur.[49]

The 1994 ATTC demonstrated that when arterial disease is taken together as a whole, occlusion is significantly reduced by 44% with the use of antiplatelet therapy, while treatment continues ($p = 0.00001$); however, when peripheral angioplasty is analysed separately a 47% non-significant reduction in occlusion is seen.[51]

Although there have been promising results in animal studies[52,53] suggesting that antiplatelet agents reduce neo-intimal hyperplasia there is no consistent evidence that conventional antiplatelet agents reduce restenosis. Several human studies of coronary artery intervention have suggested that cilostazol may reduce the restenotic process, however, these data are not supported in peripheral arterial intervention.[54,55] There is currently no evidence to support the use of other antiplatelet agents in preventing restenosis after angioplasty and stenting.

Bleeding complications. We were unable to identify any large prospective, placebo-controlled studies in peripheral angioplasty providing detailed information on local or systemic bleeding complications associated with the use of antiplatelet therapy.

The 1994 ATTC[51] demonstrated that when antiplatelet drugs were started prior to vascular intervention there was a small but significant increase in major bleeds (13 ± 4 per 1000) and the need for re-operation for major bleeding. These data are not specific for peripheral angioplasty and do not consider the adverse vascular events prevented by treatment.

Patients undergoing percutaneous coronary intervention in the CURE study were found to have a statistically significant increase in minor bleeding during their longer-term follow-up (CI 1.68(1.06–2.68) $p = 0.03$), although not within 30 days of the procedure.[56] A statistically significant increase in major bleeding or transfusion requirements was not found with the addition of clopidogrel to aspirin during the study in the PCI-CURE sub-study patients.

Recommendations
There seems to be no strong evidence to support the stopping of aspirin prior to angioplasty and stenting in patients with PAD. In addition it is recommended that patients not on aspirin, and who are candidates for antiplatelet prophylaxis should receive a loading dose of aspirin (300 mg) at least 2 h prior to the procedure. With clopidogrel, the safest option may be to start the drug immediately following the procedure. When patients are already on clopidogrel consideration should be made to stopping it 5–7 days prior to the procedure if bleeding risks are thought to be high.

Scenario 4

Antiplatelet therapy in peripheral arterial bypass surgery. (Fig. 7)

Evidence
As with peripheral angioplasty, the risk and benefit of antiplatelet therapy require careful evaluation in patients undergoing peripheral bypass surgery. In the case of surgery, the risk of cardiovascular events is higher in the perioperative period and more evidence is available on a wider range of antithrombotic agents than with angioplasty.

Reduction of cardiovascular events. In the meta-analysis by Robless *et al*., which looked at all vascular events in PAD patients, a non-significant reduction in vascular events was observed (relative risk 0.76, 95% CI 0.54–1.05) in patients undergoing lower limb bypass associated with antiplatelet therapy.[9] This may reflect a type 2 statistical error due to a lack of includable trials.

Improvement of patency. The 1994 ATTC demonstrated that vascular occlusion was significantly reduced by around 40% with antiplatelet therapy in patients undergoing coronary and peripheral arterial bypass surgery while treatment continues ($p = 0.00001$). Eleven of these trials (>2000 patients) involved patients undergoing peripheral bypass surgery and the analysis demonstrated a significant reduction in graft occlusion (38% odds reduction).[11] In a more recent systematic review of antiplatelet agent versus placebo in infrainguinal bypass, only five trials were found to be suitable for inclusion.[57] The review demonstrated a significant reduction in occlusion rates with antiplatelet agents, (risk reduction 0.78, 95% CI 0.64–0.95). A similar review by Girolami also demonstrated a significant benefit from antiplatelet drugs in preventing peripheral bypass graft occlusion.[58] Following the data cut off date for Tangelder's systematic review, the result of a large placebo controlled trial (243 patients) of ticlopidine in patients undergoing infrainguinal

Summary in evidence:

- Patients undergoing vascular surgical intervention are at an additional high risk of subsequent MI and stroke. (I)
- Continuing antiplatelet agents around the time of surgery may increase the risk of haemorrhagic complications. (II)
- Continuing antiplatelet agents around the time of vascular intervention may reduce the risk of perioperative MI. (II)
- Evidence suggests that either antiplatelet agents or anticoagulation improve the long-term patency of vascular grafts. (II)

Recommendations:

- All patients with symptomatic peripheral arterial disease or who have had previous vascular intervention should be considered for long-term anti-platelet therapy, unless contraindicated (A)
- Aspirin should be continued peri-procedure unless a particular concern over increased bleeding exists. (B)
- Consideration should be made to stopping clopidogrel 5 days prior to elective surgery. (B)

Fig. 7. Scenario 4: Antiplatelet therapy in peripheral bypass surgery.

saphenous vein bypass grafts has been published.[25] This demonstrated a significant improvement in long-term graft patency with ticlopidine. When the agents used are considered individually there is data related to aspirin plus dipyridamole, ticlopidine and warfarin[25,59–64] (Table 3).

Aspirin

Five randomised, double blind placebo controlled studies of aspirin plus dipyridamole have been reported. Meta-analysis of this data has shown a statistically significant reduction in graft occlusions with aspirin plus dipyridamole (relative risk 0.78 (0.64–0.95)).[57] Interestingly, the largest and longest duration study showed no statistically significant effect of antiplatelet drugs on graft occlusion. It is plausible that the antiplatelet effect is most important for short and medium term patency, and as time progresses, progression of the underlying disease contributes more to graft failure. It is also of note that the studies by Green and Donaldson, which both had highly significant results, only included prosthetic grafts (Table 3).

Ticlopidine

The study by Becquemen 1997 is the only blinded placebo controlled study of ticlopidine in peripheral bypass.[25] The study assesses saphenous vein graft patency, death and vascular events in 243 patients undergoing infrainguinal bypass. Graft patency was significantly improved in the ticlopidine treated patients at two years (66.4 vs 51.2%, $p = 0.02$), although there was no statistically significant reduction in death or ischaemic events.

Anticoagulation

Only one long-term placebo controlled study has been published assessing the effect of anticoagulation alone in peripheral bypass graft patency. The aim of the study was to determine whether long-term oral anticoagulant treatment was effective in improving graft performance and preventing major amputation following femoropopliteal autologous vein bypass for atherosclerosis. The trial involved a single center and continued for over 10 years. The study demonstrated that anticoagulation was superior in terms of graft patency, limb salvage, and survival (Table 3).

A controlled study showed no significant reduction in graft patency rates with oral anticoagulation during the 5-year follow up;[65] however, the study included in its randomisation patients with thromboendartectomy, central reconstruction and conservative treatment.

Antiplatelet agent versus anticoagulation

The Dutch Bypass or Oral anticoagulants or Aspirin study (BOA) was designed to investigate which of these possible treatments proved most effective following infrainguinal bypass.[66] Analysis of the data demonstrated no overall difference between the two treatments; however, when the subgroups of prosthetic and autologous vein graft were analysed, prophylaxis with oral anticoagulation favoured autologous vein graft patency (0.69; 95% CI 0.54, 0.88) and aspirin favoured prosthetic graft patency (1.26; 95% CI 1.03, 1.55). It is worth noting that a positive value favours oral anticoagulation and negative favours aspirin. Patients treated with oral anticoagulation in this study had an excess of major bleeds in comparison with aspirin treatment (Hazard ratio 1.96, 95% CI 1.42–2.71). One small study from Sarac ($n = 56$) demonstrated a significant reduction in graft occlusions with the combination of aspirin plus oral anticoagulant versus aspirin alone in patients with grafts at high risk of failure (3-year cumulative patency 74% vs 51%, $p = 0.04$). The incidence of postoperative

Table 3. Studies assessing the effect of antiplatelet agent on peripheral graft patency.

Study author	Year	Active treatment (*number pts*)	Placebo (*number pts*)	Follow up (*months*)	Graft patency relative risk (95% CI)
Aspirin					
Green[59]	1982	16 & 16 *	17	12	0.35 (0.18–0.69)
Goldman[60]	1984	22*	31	12	0.52 (0.26–1.02)
Kohler[61]	1984	50*	50	24	1.25 (0.85–2.39)
Donaldson[62]	1985	33*	32	12	0.26 (0.10–0.70)
McCollum[63]	1991	286*	263	36	0.92 (0.72–1.18)
Ticlopidine					
Becquemin[25]	1997	122	121	1997	0.77 (0.73–0.97)
Warfarin					
Kretschmer †[64]	1992	66	64	120	0.55 (0.33–0.99)

Randomised, double-blinded, placebo controlled studies, 12 months duration.
* Aspirin plus dipyridamole.
† Not blinded or placebo controlled.

haematoma was greater in the aspirin plus warfarin group (32% vs 3.7%, $p = 0.004$). Because of this limited data, on aspirin and warfarin, and the potential increased risk of bleeding complications, we cannot advocate this combination routinely.[67]

The overriding problem faced when reviewing this data is that studies to date have involved differing combinations of antithrombotic agents and bypass materials, making individual comparison of results difficult. Both antiplatelet therapy and oral anticoagulation are effective measures to maintain patency in infrainguinal grafts.[51,57,58] Previously there has been a tendency in clinical practice to opt for anticoagulation in "high risk" grafts, such as prosthetic and pedal bypasses and aspirin in the rest.

Current data would suggest that antiplatelet agents are slightly more effective than anticoagulation in the prevention of prosthetic bypasses occlusion, and anticoagulation is slightly more effective for vein graft occlusion; however, anticoagulation increases the haemorrhagic risk and poses other management issues. Vein graft thrombotic prophylaxis must therefore remain an area for local or individual decision (Fig. 8).

Risk of perioperative bleeding. In vascular surgery there are very few studies that have satisfactorily assessed the effect of antiplatelet agents on bleeding complications as part of their primary study design.[63] In a large multi-centre trial of aspirin plus dipyridamole versus placebo, 549 patients underwent saphenous vein femoropopliteal bypass.[63] No difference in patency rates was demonstrated between the groups, although a significant reduction ($p = 0.004$) in MI and stroke was observed in patients randomised to the antiplatelet drugs. However, the rate of re-operation for bleeding was almost double in the aspirin plus dipyridamole group, although this did not reach statistical significance ($p = 0.13$). Likewise there was no difference in the incidence of wound haematomas or GI bleeding.

Controversy remains as to whether patients should stop antiplatelet therapy prior to vascular intervention. There is some evidence that periprocedural antiplatelet therapy may reduce the rate of acute re-occlusion, although this may increase the risk of bleeding. Studies in coronary artery bypass have shown that the perioperative timing of antiplatelet agents is important and that antiplatelet agents can reduce mortality in patients undergoing coronary artery bypass grafting (CABG). In a large case control study of 8641 consecutive patients undergoing CABG, the odds ratio for a reduction of in-hospital mortality with preoperative aspirin therapy was 0.73 ($p = 0.03$).[68] No significant difference was seen in the quantity of chest tube drainage, transfusion requirement or need for re-exploration due to haemorrhage.

In line with the manufacturers recommendations and the findings of several studies of thienopyridines in cardiac surgery, caution must be exercised in the perioperative use of these drugs. Patients participating in the CURE study who underwent coronary artery bypass grafting had an increased risk of major bleeding if clopidogrel was taken during the 5 days preceding surgery.[44] There is likely to be an increased risk of haemorrhage associated with clopidogrel during open peripheral arterial surgery.[69]

Recommendations

In patients with PAD aspirin should be continued peri-procedure unless particular concerns exist over operative bleeding in patients undergoing surgical peripheral arterial intervention. Clopidogrel may increase operative bleeding and consideration should be made to stopping it 5 days prior to surgery. In addition to their long-term benefits in reducing rates of MI and stroke, antiplatelet agents are recommended to maintain infrainguinal graft patency. As an alternative to antiplatelet agent therapy, oral anticoagulation is an acceptable in the case of autologous

- Meta-analysis has demonstrated that overall antiplatelet agents can help prevent graft occlusion following infrainguinal bypass surgery.
- Aspirin appears more effective than anticoagulation in preventing prosthetic graft occlusion.
- Anticoagulation appears more effective than aspirin in preventing autologous vein graft occlusion.
- Ticlopidine is more effective than placebo in preventing vein graft occlusions.

Fig. 8. Antithrombotic drugs in maintaining infrainguinal bypass patency.

vein bypass and other grafts deemed at high-risk of failure (Fig. 8).

Scenario 5

Antiplatelet agents in patients with aortic aneurysms (Fig. 9)

Evidence

Although there is evidence that platelet accumulation is reduced in patients with aortic aneurysms taking aspirin there is no evidence that antiplatelet drugs reduce clinically important peripheral embolic events or aneurysm growth.[70] Data from the "U.K. Small Aneurysm Trial" demonstrated that patients with aortic aneurysms and a reduced ABPI have a particularly high mortality for cardiovascular death (66% of deaths).[71] These data also suggest that antiplatelet therapy with aspirin should be considered as the yearly risk of cardiovascular events was greater than 1.5%, such that the benefit outweighs the risk of bleeding.[43] In support of the presence of an AAA being a marker of vascular risk, the National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) – III guidelines, now consider the presence of an abdominal aortic aneurysm to be a coronary heart disease (CHD) risk equivalent ($\geq$20% cardiac events rate in 10 years).[72]

Recommendation

It is recommended that all patients with an abdominal aortic aneurysm and evidence of symptomatic PAD should receive antiplatelet prophylaxis. Patients with an aortic aneurysm, but without evidence of symptomatic PAD also have a high risk of cardiovascular events, and therefore should also be strongly considered for antiplatelet prophylaxis.

Scenario 6

Antiplatelet agents in patients with recurrent vascular events (Fig. 10)

Evidence

Information on the prevention of recurrent events in PAD patients is scarce, and we need to extrapolate from studies in IHD and CVD.

Possible causes of recurrent vascular events despite antiplatelet therapy

Drug non-compliance. Routine toxicology tests are not sensitive enough to measure therapeutic aspirin levels. In addition, aspirin has a short half-life of about 30 min and an antiplatelet effect can be detected for about 7 days after the drug has been eliminated, but clinically effective platelet inhibition may be lost sooner. Non-compliance is likely to be a significant factor in failure of antiplatelet therapy.

Aspirin resistance. It has been demonstrated that up to 25% of individuals have a reduced response to aspirin, when measured by platelet aggregation tests.[73,74] Although there is evidence that increasing the dose of aspirin may partly counteract this aspirin resistance, there is no evidence to support that increasing the dose in these individuals improves clinical outcome. A recent study evaluated urinary thromboxane concentration as an indirect marker of aspirin effect. The study demonstrated that those patients with highest urinary thromboxane concentrations had a significantly greater risk of cardiovascular death.[75]

Summary of evidence:

- The presence of an abdominal aortic aneurysm is a marker of generalised atherosclerosis and increased mortality from vascular disease. (II)
- Patients with aortic aneurysms and low ABPI's are those at highest risk of adverse cardiovascular events. (II)

Recommendations:

- Patients with abdominal aortic aneurysms and occlusive PAD should receive antiplatelet prophylaxis. (A)
- Those patients with aortic aneurysms without evidence of PAD should be strongly considered for antiplatelet prophylaxis due to their high risk of future vascular events. (B)

Fig. 9. Antiplatelet agents in patients with aortic aneurysms.

Summary of evidence:

- Data from cardiac disease suggests that the combination of aspirin plus clopidogrel is more effective than aspirin alone. (II)
- Data from cerebrovascular disease suggests that the combination aspirin plus dipyridamole is more effective than aspirin alone. (II)
- In patients with autologous venous bypass grafts, oral anticoagulant may be more effective than antiplatelet agents. (III)
- The evidence to support increasing the aspirin dose is limited. (III)

Recommendations:

In patients with recurrent vascular events despite antiplatelet therapy, the following may be considered:

- Add in another antiplatelet agent (B)
- Change antiplatelet drug (eg: aspirin to clopidogrel) (C)
- Change to anticoagulant (C)

Fig. 10. Antiplatelet agents in patients with recurrent vascular events.

Disease progression. No clear evidence exists on the effects of antiplatelet therapy on disease progression.

Possible actions for patients with recurrent vascular events are

- Continue current antiplatelet therapy (same dose).
- Increase dose (aspirin only), e.g., from 75 to 150 or 300 mg.[74]
- Change antiplatelet drug (e.g., aspirin → clopidogrel).[76]
- Add another antiplatelet agent[42,44] e.g., aspirin plus clopidogrel or dipyridamole.
- Change to oral anticoagulant. This option should be considered particularly in the case of autologous vein bypasses.[66]

Recommendation

The management of patients with recurrent vascular events represents a contentious issue particularly when identifying high-risk patients is often less than clear. Each of the above regimes may be justified based on current evidence (or lack of it). However, in the absence of good clinical trial evidence it is difficult to make recommendations, on comparative efficacy.

Scenario 7

Non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs), Renal and GI toxicity in patients with PAD (Fig. 11)

NANSAIDs and antiplatelet therapy in patients with PAD. Concomitant administration of NANSAIDs may be needed for the treatment of musculoskeletal disorders in patients receiving antiplatelet prophylaxis with aspirin. In these circumstances concern is often raised over the potential for GI and renal toxicity, in addition patients with PAD are more likely to be elderly and have renal vascular disease as part of a more generalised atherosclerotic process, and are hence at high risk of NANSAID induced renal toxicity. COX-2 inhibitors (selective NANSAIDs) have a lower risk of GI complications, but they have a similar propensity to cause renal toxicity as conventional non-selective NANSAIDs[77,78] and they may also be hazardous due to increases in blood pressure. Therefore if at all possible the NANSAIDs should be stopped in patients receiving aspirin as antiplatelet prophylaxis. In addition, there is currently no compelling data that either selective or non-selective NANSAIDs provide adequate antiplatelet effect for the prevention of MI and stroke.[79–82] All patients with symptomatic PAD taking a NANSAID should therefore also receive an effective antiplatelet drug, although with the caution that the combination of aspirin plus NSAIDs may increase the risk of GI bleeding.[83]

In two large randomised controlled trials of COX-2 inhibitors, the celecoxib long-term arthritis safety study (CLASS) was unable to demonstrate a reduction in ulcer complications in patients treated with celecoxib over patients treated with non-specific NSAIDs; in the Vioxx (rofecoxib) gastrointestinal outcomes research (VIGOR) study, GI complications were lower with rofecoxib than with naproxen, although, cardiovascular mortality was significantly increased.

Summary of evidence:

- Non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) can be hazardous in patients with peripheral arterial disease and renal impairment, due to renal toxicity. (II)
- COX-2 inhibitors may also be hazardous in patients with peripheral arterial disease due to renal toxicity (II).
- There is no convincing evidence to date that conventional or selective (COX-2) NANSAIDs provide satisfactory cardiovascular protection. (II)
- There is evidence that the combination of aspirin + NANSAIDs over aspirin alone increases the risk of gastrointestinal bleeding (II)

Recommendation:

- Patients with peripheral arterial disease, taking aspirin, should avoid NANSAIDs (including COX-2 inhibitors) if possible, particularly if they have a history of renal impairment. (B)
- Patients with peripheral arterial disease who require both a NANSAID inhibitor plus an antiplatelet drug should consider either taking aspirin and a gastroprotective drug *e.g. a proton pump inhibitor* (B), or consider changing aspirin for clopidogrel as antiplatelet therapy. (C)
- The following alternatives should be considered in a patient intolerant of aspirin for gastric reasons (following exclusion of other cause of ulceration):
  - Stop any concomitant NANSAIDs , if possible. (B)
  - Use clopidogrel instead of aspirin. (B)
  - Add a proton pump inhibitor to aspirin for gastric protection. (B)

Fig. 11. Antiplatelet agents, non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs), Renal and GI toxicity in patients with PAD.

Subsequent analysis of the data from VIGOR with other phase IIb and III trials of rofecoxib have suggested that this increase in mortality relates more to naproxen's antiplatelet activity rather than an increase in cardiovascular events of rofecoxib.[84] Differences in trial design and comparative drugs make direct comparison between CLASS and VIGOR difficult.[85,86] Guidance from U.K.'s National Institute of Clinical Excellence (NICE) on the use of COX-2 inhibitors suggests that they are used in preference over conventional NSAIDs, in patients at high risk of GI complication including those over 65 years. They also state that "in patients taking low dose aspirin, the benefit of using COX-2 selective agent (to reduce GI toxicity) is reduced". Prescribing COX-2 selective agents preferentially over standard NSAIDs in this situation is therefore not justified on current evidence.[87]

GI intolerance of NSAIDs

Patients with PAD, are likely to have at least one of the risk factors for cyclo-oxygenase inhibitor induced GI complications.[88] To date there have been no randomised trials on the effect of acid suppression on cyclo-oxygenase inhibitor associated complications, although studies have shown that proton pump inhibitors (PPI) are protective, and long term studies have shown them to prevent gastric and duodenal ulcers. There may also be benefits in screening for and treating *Helicobacter pylori* infections in patients receiving long term NANSAIDs.[89,90]

Not all conventional NSAIDs appear to have the same risk of GI toxicity. A meta-analysis by Henry *et al*.[91] evaluated the variable risk of GI complications with individual NSAIDs. The meta-analysis demonstrated that ibuprofen had the lowest risk of GI complications. Although this study does not examine the comparative risk of each drug when combined with aspirin, it is still a useful base to select a low risk NSAID. However, new work suggests that some COX-2 inhibitors may reduce the antiplatelet effect of aspirin.[92] In this study, the concomitant administration of ibuprofen but not rofecoxib, acetaminophen or

diclofenac antagonised the irreversible platelet inhibition induced by aspirin.

As an alternative to prescribing aspirin plus a gastroprotective drug in patients with aspirin induced GI toxicity, or as an alternative to the concomitant prescription of aspirin plus NANSAID, clopidogrel may be substituted for aspirin. Data from the CAPRIE study, demonstrated that clopidogrel had a lower risk for GI bleeding complications than aspirin; in addition, clopidogrel has been shown to be associated with less gastric irritation than aspirin.[93] Clopidogrel may be a preferred alternative to aspirin in patients taking NANSAIDs, but no trial evidence supports this option. Both changing the antiplatelet agent and the co-prescription of a gastroprotective drug have cost as well as clinical implications.

Cost Issues

The principle objective of this consensus was to assess the evidence for antiplatelet drug efficacy in clinical practice rather than to perform a cost analysis. Although we appreciate that drug cost is a highly important aspect to the effective delivery of limited health care provisions, the resources required to accurately identify the total "costs" of drugs was beyond the scope of this consensus group in terms of time, skills and funding. Overall, long-term antiplatelet therapy appears a cost-effective strategy for the prevention of MI, stroke and arterial re-occlusion following therapeutic interventions in patients with symptomatic PAD.[34] Insufficient data exists on the absolute costs of aspirin in comparison with alternative antiplatelet drugs, particularly when the adverse events are taken into account. In a meta-analysis by Hankey[76] it was estimated that by substituting clopidogrel for aspirin among high-risk patients, between two and 19 patients may be prevented from having one or more recurrent vascular events per 1000 patients treated; however, aspirin is cheap while alternatives are more costly. We recommend further studies of cost-effectiveness of different antiplatelet therapies/combinations in PAD patients.

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Conflicts of Interest

The consensus meeting was funded by an educational grant from Sanofi~Synthelabo. Pharmaceutical representatives were not present during any part of the meeting and were not involved in planning the agenda or structure of the meeting. The choice of participants and the meeting's conclusions were made without financial influence from outside bodies. No payment was made to participants either to attend the meeting or to review the findings (although expenses were paid). Several of the contributors have, however, received sponsorship and honorariums in the past from a variety of companies related to antiplatelet drugs and PAD.

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Accepted 5 March 2003